# FUNCTIONAL MICROSTIMULATION OF THE LUMBOSACRAL SPINAL CORD

**Contract NIH-NINDS-No1-NS-2-2342**

**Quarterly Progress Report #3**
Period covered: 1 July 2002 to 30 September 2002

Submitted to:
Neural Prosthesis Program
National Institute of Neurological Disorders and Stroke
National Institute of Health

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## ABSTRACT

The main aim of this contract is to test the idea that intraspinal microstimulation (ISMS) can be used selectively to excite neurons that activate the bladder detrusor muscle while simultaneously stimulating interneurons which inhibit motoneurons of the external urethral sphincter (EUS). If this reciprocal action works well enough to produce bladder voiding after spinal-cord-injury (SCI), it could form the basis of a neuroprosthesis that would restore bladder control without the need for transection of sensory nerve roots of the spinal cord (dorsal rhizotomies).

In this third quarter of operation the following was achieved:

1) Chronic implants of ISMS microwire arrays were performed in three cats additional to the one referred to in the last quarter. Satisfactory chronic ISMS data were obtained in two cats: Rusty (implanted 02 July 2002) and Mick (implanted 01 October 2002).

2) Two types of headpiece were implanted and compared with the backpack described in Quarterly Report #2.

3) A new indwelling bladder catheter was designed, fabricated and chronically implanted.

4) In the two successful chronic implants, the following effects of ISMS were noted:
   - Increases in bladder pressure of up to 40 mm Hg were elicited by ISMS in the awake animal without any signs of discomfort.
   - The increments in pressure elicited were highly dependent on the background bladder volume and pressure.
   - The bladder contractions in the conscious animals were accompanied by intra-urethral EMG responses or perineal co-contraction, which seemed to limit voiding.
   - ISMS through the microwires implanted in the dorsal commissural region that inhibits urethral activity, tended to elicit aversive reactions at fairly low stimulus strengths in the awake animal, as first noted in our last quarterly report. This meant that the testing of ISMS in the urethral-inhibitory region had to be restricted to stimulus levels below those eliciting aversive reactions. Concomitant ISMS in the bladder-excitatory and urethral-inhibitory regions was tested in the final chronic cat.

## PROGRESS IN THIS QUARTER

### METHODS

*Anesthesia and Monitoring of Vital Signs*

Four male adult cats were used in the experiments. The surgery was performed in a fully-equipped operating room with sterile equipment and procedures. The cats were anesthetized with 2-3% isoflurane in carbogen: (95% $O_2$, 5% $CO_2$), 1.5 L/min. Anesthesia was maintained through a pediatric endotracheal tube. An intravenous catheter was inserted in the cephalic vein and a saline drip was delivered throughout the procedure. The cats' body temperature was maintained using heating pads and lamps. ISMS microwires were implanted in the sacral spinal cord, a catheter was implanted into the bladder, and in two cats, in-dwelling wires were implanted into the urethra for the purposes of measuring EMG or to allow intra-urethral stimulation.

Two of the four chronic implants were terminated earlier than scheduled. In the first of these (Lou, 6 September 2002), ISMS thresholds were above 0.5mA in the days immediately following surgery. At four days post-operative, a dissection revealed that the microwire bundle had been accidentally severed during the original surgery. The second implant (26 September 2002) was abandoned during surgery due to major difficulties implanting a Foley catheter into the bladder.

*Implantation of Urinary Tract Monitoring Devices*

As just mentioned, problems were encountered with the Rusch 2 mm Foley catheter described in Quarterly Report #2. Difficulties were encountered inserting the catheter through the bladder wall at the dome of the bladder, leading to unacceptable trauma to the bladder requiring the cat to be euthanized. The Foley catheter implanted in cat #1 (Rusty) had a bulky valve side-arm that was implanted sub-cutaneously (see previous Quarterly Report). A proliferation of connective tissue was noted around this structure in a post-mortem dissection. This may have contributed to the urge-incontinence described in this animal in the previous report.

Consequently, in this quarter we designed and tested a silastic catheter with a smaller diameter, and a cone close to the tip, which served to anchor the tip of the catheter within the bladder (Fig. 1). Implantation of this new catheter was performed in the same way as described previously for the Foley catheter. The bladder was exposed through a midline abdominal incision. A stylette was inserted into the tip of the catheter through the side-

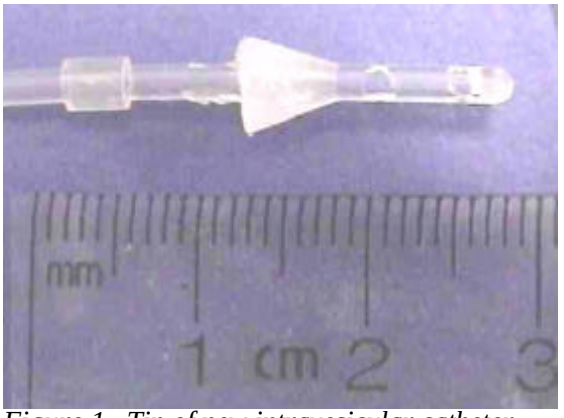

*Figure 1. Tip of new intravesicular catheter, showing retaining cone and washer*

port (Fig. 1) and the tip, including the cone, was inserted into the bladder through a puncture hole created with a 16G hypodermic needle. The stylette was withdrawn without pulling the catheter out. A purse-string suture (4/0 prolene monofilament) in the bladder wall was placed around the catheter between the cone and the washer, to hold the catheter in place (Fig. 2). The free end of the catheter was tunneled subcutaneously to emerge through a skin incision on top of the cat's head.

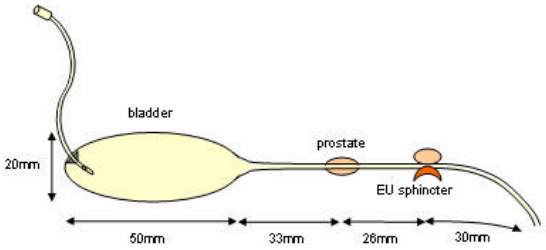

*Figure 2. Bladder catheter location.*

*Intraurethral EMG electrodes and pressure measurements*

In the first two cats we implanted intra-urethral wires to allow either EMG recording or stimulation within the urethra. The surgical approaches we used are shown in Fig. 3. In the first, the EMG wires were introduced into the urethra through a puncture hole in the bladder neck (Fig. 3A). In the second, the wires entered the dome of the bladder and were coiled within the bladder to provide strain relief when the bladder expanded and contracted (Fig. 3B). In both cases the wires were inserted through a Kendall Argyle 5 Fr. (1.7mm) feeding tube that had been fed from the tip of the penis through the urethra towards the bladder. When the tip of this tube reached the interior of either the bladder neck or the bladder wall a small incision was made over it and it was pushed through the wall. Pairs of Teflon-insulated Cooner AS631 stainless steel multi-stranded wires de-insulated for ~5mm at their ends were threaded into the side-port of the tube which was then drawn back into the urethra and out of the penis, carrying the Cooner wires with it. The wires were freed from the tube, separated and pulled back into the urethra by about 25mm and 35mm respectively which located them on either side of the EUS (which we had determined by previous dissection is about 30mm from the tip of the penis in a 3 Kg cat). Cyanoacrylate glue was used to seal the puncture hole in the bladder neck or dome of the bladder where the wires emerged, and also served to anchor the wires in place. The free ends of the wires terminated in a silastic-coated DIL connector which was pulled sub-cutaneously to the backpack or headpiece inside a trochar. During recording sessions this connector connected to cables leading to a Neurolog EMG amplifier. EMG signals were amplified (gain 1000, bandpass filtered (30 – 2,000 Hz) and

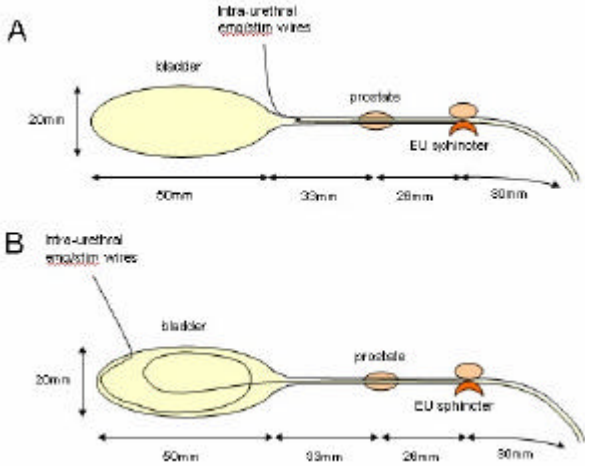

*Figure 3. Chronic implants of intraurethral EMB/stimulation wires. A: wires implanted through bladder neck B: wires implanted through dome of bladder and coiled inside bladder to adapt to bladder filling.*

digitized at a rate of 4,000 samples per second using a CED Power 1401 (Cambridge, UK) hardware and Signal 2.1 software. The pressure signal was low-pass filtered at 30 Hz and sampled at the same rate. The data were stored on the computer's hard drive for later analysis.

*ISMS: Locating targets in the Sacral Spinal Cord*

Before inserting the ISMS microwire arrays, a series of penetrations through the dura was performed with a search electrode (30 µm stainless steel microwire, 3.5 mm depth). Short (~0.5s) pulse trains of up to 300µA were applied. The responses of interest were changes in bladder pressure, EUS EMG and contractions of intrinsic toe muscles and hamstrings muscles biceps femoris posterior and semitendinosus (PBSt). When bladder-excitatory and EUS-inhibitory regions had been located, an 8/0 ophthalmic suture was sewn into the dura mater to act as a marker for the placement of the microwire array.

Once the regions of the target nuclei were determined, arrays of 16 stainless-steel microwires were implanted and fixed in place using droplets of isobutyl cyanoacrylate. A custom-made multi-channel microstimulator was used to deliver ISMS through each electrode in turn (Prochazka et al. 2002). Typically microwires targeting the EUS inhibitory region were inserted 2.5 mm from the dural surface (~1.5 mm from the cord dorsum surface) and those targeting the bladder preganglionic neurons 3.5 mm from the dural surface (~2.5 mm from cord dorsum surface).

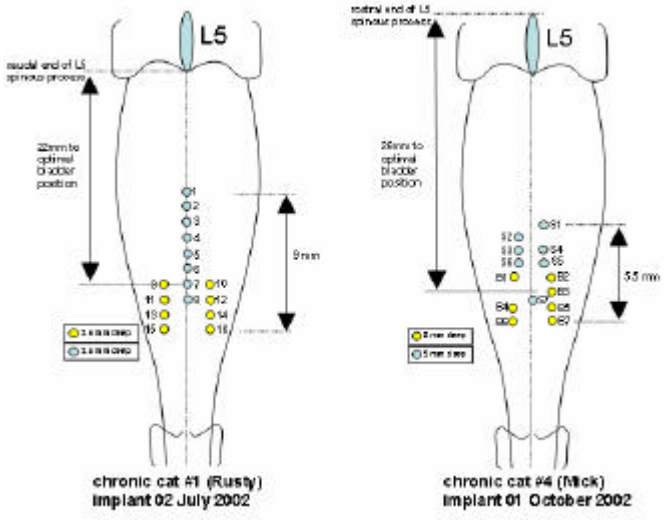


*Figure 4 Positions of ISMS microwires in the two successful chronic implants.*

*Backpack and head-piece*

After the ISMS microwires had been implanted in the spinal cord, the paravertebral muscles, lumbo-dorsal fascia and skin were sutured closed in layers. The microwire connector was pulled subcutaneously to the backpack or headpiece. The backpack was described in detail in our previous report. The headpiece was fashioned out of dental acrylic anchored to the skull by four stainless steel screws (Prochazka 1984). The Luer hub of the bladder catheter along with the EMG and microwire connectors were embedded in the acrylic.

## RESULTS

*Chronic implants*

Results from the first chronic implant were presented in the previous report. In the second implant, the microwires were accidentally transected as mentioned above, so no ISMS results were obtained. Post-operatively the cat's overall condition was satisfactory, but as in the first chronic implant it voided frequently. Urine analysis was performed and no infection was found. Urge incontinence persisted until day 4 when the animal was euthanized with pentobarbital. Post-mortem dissection did not reveal any obvious infections around the bladder and urethra. In the absence of other indications we therefore attributed the urge incontinence to the presence in the bladder and urethra of the catheter and/or intra-urethral EMG wires.

The third chronic implant was aborted, as mentioned above. In the fourth implant (second successful chronic implant), we omitted the intra-urethral wires, to eliminate one of the possible sources of urge incontinence. Although excellent results have been obtained with ISMS for over three weeks in this animal (results below), this cat also exhibited urge incontinence for the first two weeks, with frequent voiding. Urine and blood tests were negative for bacterial infection, but as a precaution, a two-week course of the broad spectrum antibiotic Clavimox was administered. There was no sign of edema or tenderness around the spinal implant or headpiece, so at this point the bladder catheter remains the likely cause of the urge incontinence in both successful chronic implants.

*Results of ISMS*

Fig. 5 shows three examples of large increases in bladder pressure elicited in this cat with ISMS delivered through one or more of the microwires located as shown in the inserts. These results were obtained 3 days after the implantation procedure. No voiding occurred in any of these trials, indicating that urethral co-contraction probably took place, retaining urine in the bladder despite the large

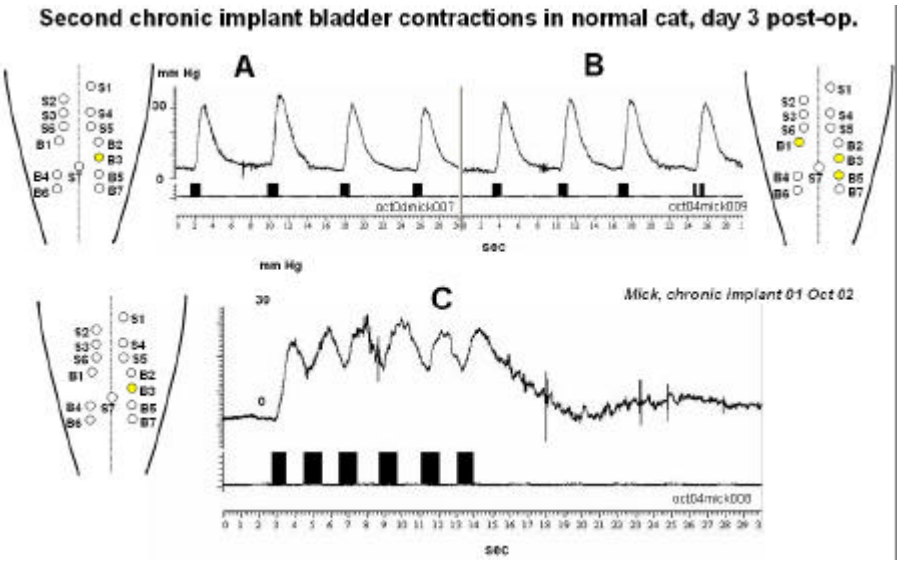


*Figure 5 Bladder contractions evoked in the awake cat with ISMS (interleaved trains) delivered through implanted microwires targeting the bladder excitatory region. The locations of the active microwires are shown as yellow-filled circles in the schematics next to each panel.*

increases in bladder pressure. As in the first successful chronic implant, this cat showed no orienting or aversive responses to stimulation in the bladder excitatory areas at intensities sufficient to evoke these large responses.

Fig. 6 shows similar results to Fig. 5B, obtained 9 days later with identical stimulus current settings through three the same three microwires located in the bladder excitatory region. These reproducibility of the results indicates that the fixation of the microwires was sufficient to prevent any significant shifting in the positions of the stimulating tips during activities of daily life over this period.

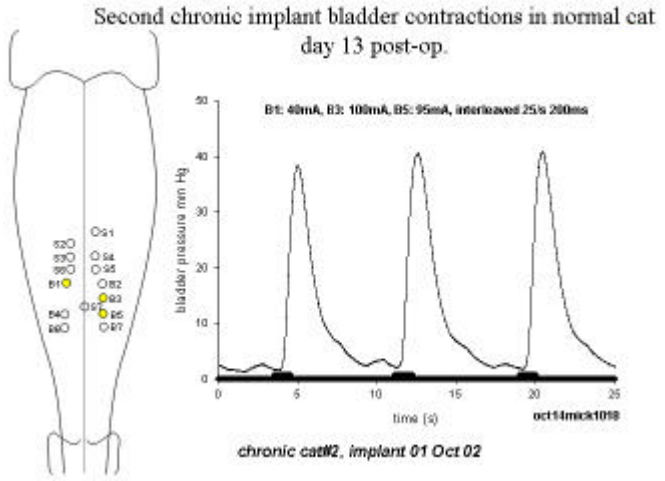


*Figure 6 Bladder contractions evoked in the awake cat with ISMS (interleaved trains) delivered through implanted microwires targeting the bladder excitatory region. Same cat as in Fig. 6, 13 days post-operative.*

Fig. 7 shows the results of two sets of overlapping bursts of ISMS applied first through three microwires in the bladder excitatory region (interleaved 25/s spike trains) followed by ISMS through three microwires targeting the dorsal commisure EUS inhibitory region (locations shaded green). The aim here was to relax the EUS at the peak of bladder pressure to facilitate voiding. Only a few drops of urine were produced, which indicates that if the EUS was indeed inhibited, it was insufficient to be useful from a functional point of view, at least in the normal cat with reflexes intact.

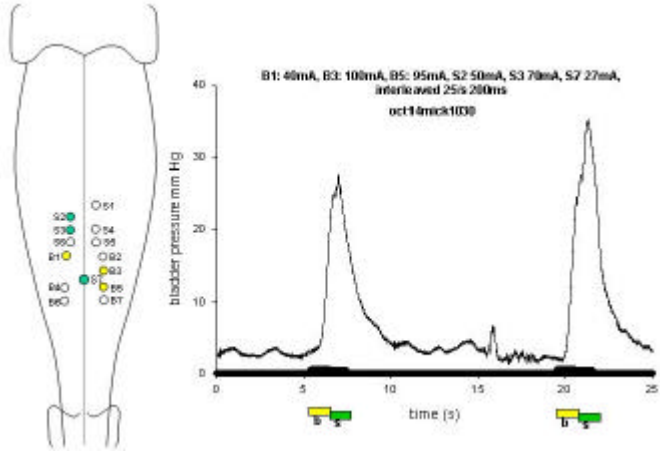


*Figure 7 Bladder contractions evoked in the awake cat with ISMS (interleaved trains) delivered through implanted microwires targeting the bladder excitatory region. Same cat as in Fig. 6, 13 days post-operative.*

*<u>Sensory perception of ISMS</u>*

Whereas stimulation through the bladder-excitatory microwires went largely unnoticed by the animal (at most a casual turn of the head at peak bladder pressure, possibly due to sensory input from the bladder itself), stimulation through the microwires implanted in the dorsal commisure elicited orienting movements at significantly lower currents

(range 35 – 100 μA). We were careful to increase the stimulus strength through these microwires very slowly. Typically the responses were head-turning, and at slightly higher stimulus levels, licking of the perineal region, and on a small number of occasions a single vocalization. At the first sign of a clear aversive reaction such as this, the stimulus levels were reduced by about 10%.

## DISCUSSION

The main technical developments this quarter were the improved bladder catheter and the switch from a back-pack to a head-piece for the connectors and catheter. The Foley catheters used in the first two chronic implants were fairly bulky and led to the formation of adhesions and a connective tissue mass in the vicinity of the bladder. This may have been responsible for the urge incontinence seen in these animals. The smaller catheter used in the final implant was easier to insert, and had a much smaller profile as judged by external palpation. Urge incontinence still occurred in this cat in the first two weeks post-operatively, but this seems to have resolved at the time of writing (4 weeks post-operatively). The back-pack connector of the first successful implant loosened slightly after a few days, and tended to draw the cat's attention, for example when it rolled over onto its back. The headpiece proved to be more convenient and remained essentially ignored. Head-pieces will be used exclusively in the future.

The two successful chronic implants represent the first time that ISMS via implanted microwires has been performed in the normal, awake animal (note that in the pioneering chronic ISMS implant studies of Friedman et al. the animals were all lightly anesthetized during stimulation trials (Friedman et al. 1972)). The significance of observing the effect of ISMS in the normal animal this is that we were able to gain an idea of the sensory perceptual thresholds of ISMS in the bladder excitatory region compared to the dorsal commisure (putative EUS-inhibitory region). Perceptual thresholds, judged by the appearance of orienting reactions, were significantly lower in the commisure in both animals. In general the thresholds were just over those required to elicit reductions in urethral EMG. This may mean that stimulation in the dorsal commisure would be perceived by patients with incomplete SCI with preserved sacral sensation. It is too early to say whether the sensations evoked would be uncomfortable in humans and whether this would preclude this form of ISMS clinically. It is worth noting that dorsal column stimulation, which is also perceived in many cases, is not generally painful. On the contrary, it is a wide-spread and fairly successful technique for reducing pain and spastic hypertonus (Waltz 1997). Fig. 8 shows an estimate of the cross-sectional area around a microwire tip within which neurons might be activated by

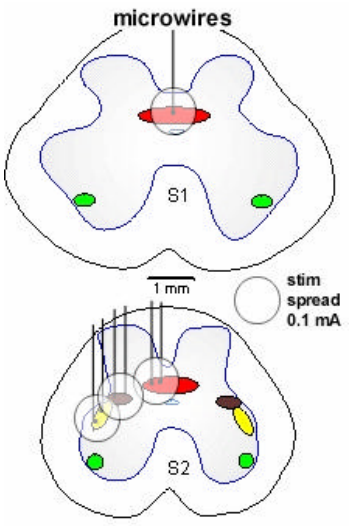


*Figure 8. estimated zones around stimulating tips in which neurons are activated by ISMS pulses of 100 mA.*

100 μA stimuli, based on the relation 180μA/mm$^2$ (Jankowska et al. 1975). Stimuli within the bladder preganglionic nucleus in the ventrolateral quadrant of the spinal cord is unlikely to activate neurons in the dorsal horn, the dorsal columns, or even second-order spinothalamic neurons crossing in the intermediate gray matter. On the other hand, stimulus spread around sites within the dorsal commisure might well impinge on any or all of these sensory areas.

On the positive side, large increases in bladder pressure were evoked by ISMS in the vicinity of the preganglionic parasympathetic nucleus without evoking orienting reactions. These contractions would suffice to void the bladder in the absence of significant urethral contractions. The clinical significance of this is that ISMS of bladder-excitatory regions may provide selective control of bladder contractions without activating EUS motoneurons. It remains to be seen whether combinations of ISMS in these regions can be found that enable efficient voiding. The situation may also change after SCI.

## PLANS FOR THE NEXT QUARTER

Three chronic ISMS implants in Edmonton

- Characterize the types of bladder and sphincter responses elicited by multichannel ISMS in the sacral region in the awake animal, particularly in relation to bladder volume.
- Concentrate on eliciting urethral inhibition, either with ISMS or intra-urethral stimulation in combination with bladder contraction to elicit voiding.
- Send first implanted cat to Halifax for testing prior to spinalization.

## ACKNOWLEDGEMENTS

We are grateful to Mr. Jan Kowalczewski, Mr. Dominic Carney and Mr. Robert Gaunt for participating in some of the technical developments and some of the experiments. We are also grateful to Mr. Allen Denington for his valuable help in all aspects of this work.

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